REMARKS

Applicants have the following comments in support of this amendment and in response to the Office Action of October 2, 2007.

Claim Amendments

The claimed pharmaceutical compositions of the present application are directed to formulations of a new and novel highly-halogenated halogenated xanthene that is fully substituted with iodine and bromine atoms (i.e., 4,5,6,7-Tetrabromoerythrosin) and which the inventors of the present application were the first to have conceived. The inventors have further created a chemotherapeutic pharmaceutical composition consisting of this novel halogenated xanthene.

As explained herein, while Applicants traverse the rejections in the Office Action, in order to advance prosecution of the present application, Applicants are amending independent Claims 1, 36 and 37. Independent Claims 1, 36 and 37 have been amended to limit the scope of the claimed injectable composition to those formulated using 4,5,6,7-Tetrabromoerythrosin. The composition of matter represented by this key active ingredient is novel in light of all known prior art.

As explained below, the pending claims are in an allowable condition, and it is respectfully requested that they be allowed.

Novel Composition of Matter

Amended independent Claims 1, 36 and 37 are directed to various injectable pharmaceutical compositions that contain a new and novel, highly-halogenated halogenated xanthene (i.e., 4,5,6,7-Tetrabromoerythrosin), which is not believed to have been described or suggested in the prior art, especially that art cited by the Examiner in this or any of the prior actions for this application. As explained below, this compound is not an obvious extension of those compounds previously known. Applicants have previously submitted the Declaration of Dr. Peter Hersey in support of the novel and non-obviousness of this and several related compounds.[1] The Examiner dismisses the Hersey Declaration as an opinion. Dr. Hersey, however, is one skilled in the art, and his opinion as one skilled in the art must be taken into consideration as evidence in support of the patentability of this application. This is especially true with regard to his expert opinions that the present compound is not the result of routine experimentation. See infra.

Prior art discussed in detail in prior amendments of this application include the Colour Index[2] and Heitz.[3] While both of these documents describe certain halogenated xanthenes, including a very extensive listing in the Colour Index, none of these references describe, disclose or suggest 4,5,6,7-Tetrabromoerythrosin, which requires substitution of the parent compound fluorescein with bromine atoms at each of the 4, 5, 6 and 7 positions *and* with iodine at each of the 2', 4', 5' and 7' positions. This represents substitution with 8 halogens at the 8 available sites for substitution, and moreover in a highly specific pattern. In contrast, despite the lengthy, comprehensive listing of compounds in the

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[1] The Declaration of Dr. Peter Hersey was submitted with Amendment I in this application on July 5, 2007.

[2] This document was previously made of record in this application. Heitz, which has been relied upon by the Examiner to reject the present application, references the Colour Index in those portions relied upon by the Examiner.

Colour Index, only five of the compounds listed have 5 or more halogens at any of these positions, and none of these contain *both* iodine *and* bromine, as in Applicants' claimed compound. Thus, the Colour Index (and Heitz) does not disclose Applicants' claimed compound or any closely related compounds. A complete listing of the fluorescein analogs in the Colour Index, along with Applicants' claimed compound, was provided in Table A of Amendment I in this application.

The previously cited prior art (as exemplified by the Colour Index) does not describe nor is it remotely similar to Applicants' claimed compound. For example, none of the listed compounds contain four iodine atoms at positions 2', 4', 5' and 7' *along with* bromine atoms at each of positions 4, 5, 6 or 7, as in the claimed compound. Thus, the prior art does not disclose or suggest Applicants' novel compound 4,5,6,7-Tetrabromoerythrosin, which is the basis for the claimed pharmaceutical compositions. See also Hersey Declaration ¶7.

In the present Office Action, the Examiner cites for the first time Walker (US 3,563,750), which also lists certain halogenated xanthenes. Each of the compounds cited by Walker is also contained in the Colour Index. Walker references the "Color Index" at col. 3, lns. 34-50. Thus, Walker also fails to describe, disclose, or suggest a compound remotely close to that of Applicants' amended claims. In the subsequent passage cited by the Examiner in the present Office Action (Walker, col. 3, lns. 50-75), Walker states that "[t]he preferred sensitizers have from 2 to 4 X=Br or I and from 0 to 2 Y=Cl substituents." Thus, Walker teaches that the preferred compounds have from 0 to 2 chlorine atoms at the 4, 5, 6 or 7 positions, whereas Applicants' claimed compound has a bromine atom at each of these positions (i.e., 4 Y = Br). Consistent with these teachings, Walker does not list a single compound in the passage at col. 3, lns. 34-50 that has even a single bromine

[3] All fluorescein analogs listed by Heitz are described in detail in the Colour Index.

atom at any position 4, 5, 6 or 7. Further, at col. 3, lns 72-73, Walker states that preferably chlorine is in these positions. Thus, the claimed compound of the present application is not disclosed or suggested in Walker but is patentably distinct from any compounds contemplated by Walker.

The Examiner also relies upon Gee. However, as discussed infra, this reference was raised in the Final Rejection of February 7, 2006. Applicants addressed this reference in Amendment G filed on August 4, 2006. In the subsequent Office Action, the Examiner no longer relied upon or cited Gee.

The novelty of the compounds claimed by Applicants is the result, at least in part, of the relative complexity of synthesis of this new compound that is posed by steric hindrance[4] from the dense content of halogens, along with other factors such as photochemical instability that make such compounds relatively difficult to produce, handle, store and use. Applicants submit that they are the first to invent the claimed new compound which represents a novel member of the halogenated xanthene family. For example, Rose Bengal (a very stable molecule which formerly comprised the most halogen-rich member of the halogenated xanthene family) has been known for over 100 years. Nonetheless, knowledge of its properties and those of the other previously known halogenated xanthenes (such as Phloxine B, Erythrosin, and Eosin) has not led those skilled in the art (prior to Applicants' conception) to conceive, suggest, synthesize or investigate Applicants' claimed highly-halogenated halogenated xanthene. See e.g. Hersey Declaration ¶11. Nor has anyone else conceived of pharmaceutical compositions consisting of halogenated xanthenes for any

[4] Steric hindrance is spatial interference inhibiting or preventing the close arrangement of adjacent atoms within a molecule due to the sizes of the overlapping electron clouds of the adjacent atoms, and poses particularly difficult synthetic challenges when large atoms, such as bromine and iodine, are incorporated into a molecule.

chemotherapeutic treatment prior to Applicants' work. Id.

As Dr. Hersey explains, the claimed compound is the result of a highly specific pattern of chemical substitution. Hersey Declaration ¶8. It is highly unlikely one skilled in the art would have arrived at such compound, unless one already knew the compound. For example, the claimed compound requires substitution of the parent compound fluoresce with bromine atoms at each of the 4, 5, 6 and 7 positions *and* with iodine at each of the 2', 4', 5' and 7' positions. This represents substitution with 8 halogens at the 8 available sites for substitution, and moreover in a highly specific pattern. None of the compounds in any of the references disclose this structure. Therefore, to arrive at this structure, one would have to take one of the disclosed structures and make numerous substitutions (the possible combinations are believed to be over 5 million) to arrive at the claimed compound. This is not the mere substitution of one element for another, and in the expert opinion of Dr. Hersey, is not routine experimentation. See Hersey Declaration ¶8. In fact, other than by blind luck, it would take many lifetimes of experimentation to substitute compounds into what is disclosed in the cited references to arrive at the claimed compound. See Hersey Declaration §9. The expert opinion of Dr. Hersey clearly rebuts the Examiner's unsupported conclusion that this is more substitution and routine experimentation. Hence, it would be nearly impossible to start with the broad, general disclosure in Heitz or the other cited references and then arrive at the claimed compound.

Applicants conceived of this new compound in an effort to improve chemotherapeutic treatment of diseases of human tissue, the performance of which may be enhanced by increasing the halogen density of the halogenated xanthene molecules, for example by including greater numbers of halogen atoms or increasing their atomic number. A consequence of such enrichment is greatly

reduced stability of the xanthene molecule, especially upon exposure to optical radiation. Such trends in synthetic complexity and instability run counter to the teachings of the prior art (such as that of Heitz) which are predicated on use of relatively stable, inexpensive molecules. For example, in the case of Heitz, which concerns certain food additives for livestock, since such animals are unlikely to be fed in the dark, investigators such as Heitz presumably would not consider developing or using photochemically unstable analogs of the halogenated xanthenes, nor would they likely select new analogs requiring complex (and presumably relatively expensive) synthesis. In the case of the Colour Index, this reference is primarily concerned with molecules of value for use as dyes. Since dyes generally must be stable in the presence of light (a dye is of dubious value if it must be kept and used in the dark since it requires light to be seen), as with Heitz, this reference would not be expected to be concerned with the relatively unstable molecules discovered by Applicants. And in the case of Walker, which is concerned with phototrophic compounds to be used in window coatings and the like, Applicants' exotic, photochemically unstable molecule is not likely to be of interest.

Hence, prior investigators had no reason and were not motivated to consider or investigate, and there is no evidence that they conceived of or considered, Applicants' novel compound since this compound would have no obvious relevance for such prior investigators.

Accordingly, the claimed highly-halogenated halogenated xanthene, and the various claimed pharmaceutical compositions containing this highly-halogenated halogenated xanthene, of the claims of the present application are novel over the prior art.

Applicants will now specifically address the Examiner's sole rejection in the Office Action.

Claim Rejections – 35 USC §103

In the Office Action, the Examiner rejects Claims 1, 9-11, 36 and 37 under 35 USC §103(a) as being unpatentable over Heitz and in view of Walker (US 3,563,750) and Gee. This rejection is respectfully traversed.

As stated *supra*, while Applicants traverse this rejection, in order to advance the prosecution of this application, independent Claims 1, 36 and 37 have been amended to be drawn to a more preferred embodiment of Applicants' invention, consisting of injectable chemotherapeutic pharmaceutical compositions of 4,5,6,7-Tetrabromoerythrosin. As explained *supra*, neither Heitz nor Walker describe, disclose or suggest Applicants' claimed compound or compositions. Similarly, Gee also fails to describe, disclose or suggest Applicants' claimed compound or compositions.

As shown herein, this case is similar to the recent Federal Circuit decision Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., 2007-1223 (Fed. Cir. March 31, 2008) (a copy which is attached herewith). Similar to that case, this application does not involve a finite (and small in context of the art) number of options easily traversed to show obviousness. See page 9 of the opinion. Instead, with regard to Heitz, there are over 5 million possibilities, and with regard to Gee, there appear to be 2.2 trillion possibilities. Similar to that case, there is nothing in the record that shows how one would start with a compound and have some reason to select (among many unpredictable and unstable alternatives) the exact route of the 8 substitutions necessary to arrive at the claimed compound. Further, the features and properties of the claimed compound (for chemotherapeutic treatment) are far afield from the purposes of the cited references. See page 9 of the opinion. There is nothing to support an inference of obviousness. As in Ortho-McNeil, the only way to arrive at the claimed invention and its properties is through hindsight reconstruction. While

that may seem logical now to the Examiner, as in Ortho-McNeil, the inventors' insights in this complex field with unstable compounds cannot be discounted. See page 10 of the opinion. As established in Ortho-McNeil, it is inappropriate here to simply trace the retrace the inventors' path, though hindsight based on the claimed invention, discounting the number and complexity of alternatives, and conclude that the claimed invention was obvious. Id.

As the record herein shows, there is nothing that would have directed one skilled in the art to the claimed compound from the cited references. Accordingly, the rejection is improper and should be withdrawn.

In addition to the above reasons regarding the impropriety of this rejection, Applicants have the following further reasons why the cited references do not disclose or suggest the claimed invention and the rejection is improper.

Heitz

As evidenced by the listing of compounds cited in Table A of Applicants' Amendment I, neither Heitz nor the reference cited in Heitz (i.e., the Colour Index) discloses or suggests the claimed compound, nor the pharmaceutical compositions of which it is a part.

Applicants believe that it cannot be disputed that Heitz does not specifically disclose the claimed compound. The Examiner, however, contends that "the compositions of Heitz et al. include the 'high halogenated xanthene' compounds and compositions according to the present invention." More specifically, it appears that the Examiner is contending that the known halogenated xanthene dyes in Heitz can be manipulated by various substitutions at eight positions to arrive at Applicants' claimed halogenated xanthene and that the vague disclosure in Heitz encompasses the claimed

compound.

It is respectfully submitted that such a rejection is improper under the patent rules.

In particular, the Examiner agrees that Heitz does not expressly disclose 4,5,6,7-Tetrabromo-erythrosin and therefore, cannot be an anticipation rejection (such a rejection having been previously withdrawn). See e.g. MPEP 2132.02. The Examiner, however, cites Heitz as disclosing a formulation comprising derivatives of fluorescein and argues that these derivatives may have one or more substituents in the 4, 5, 6, 7, 2', 4', 5' and 7' positions selected from the group consisting of fluoro, chloro, bromo, iodo, and etc. The Examiner then contends that this formulation encompasses 4,5,6,7-Tetrabromoerythrosin.

Heitz discloses at col. 4, lines 21-26 (which is relied upon by the Examiner in the Office Action) "[t]he derivatives of fluorescein (C.I. No. 45350) having one or more substituents in the 4, 5, 6, 7, 2', 4', 5' and 7' positions selected from the group consisting of F, Cl, Br, I, --NO_2, --COOH and --OH are especially important." Hence, Heitz is discussing the possibility of substitution at one or more of 8 positions with one of 7 different elements or functionalities. As the Examiner must agree, this clearly is not the limited class discussed in MPEP 2131.02. In fact, it is believed that there are over 5 million possible combinations in this disclosure in Heitz. See Hersey Declaration ¶9. A 1 in 5 million possibility is not a situation where one skilled in the art could at once envisage the claimed compound of the present application. It represents more than a finite and small number of options, similar to the Ortho-McNeil case. Only through the use of hindsight reconstruction using the claimed compound as a blueprint or endless experimentation could one skilled in the art arrive at the claimed compound from this disclosure in Heitz. As the U.S. Supreme Court warned in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727, 1742 (2007), "[a] fact finder should be aware, of

course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."

Since the present rejection is based on alleged obviousness under 35 USC §103(a), MPEP 2144.08 provides a guide for the Examiner in making such a rejection which includes following the factors set out by the U.S. Supreme Court in Graham v. John Deere. Such an analysis does not appear to have been conducted in this rejection. As noted in MPEP 2144.08, the mere fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient to establish a prima facie case of obviousness. See In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed Cir. 1994). Baird is especially on point with regard to this case (Applicants previously provided the Examiner with a copy of this case for the Examiner's review). In Baird, the Federal Circuit found that "[w]hile the Knapp formula [prior art] unquestionably encompasses bisphenol A [of claimed compound] when specific variables are chosen, there is nothing in the disclosure of Knapp suggesting that one should select such variables." 29 USPQ2d at 1552. The Court then held that "[a] disclosure of millions of compounds does not render obvious a claim to three compounds..." and reversed the obviousness rejection. The Examiner does not address this legal precedent in the rejection of the claims.

In this case, as explained above and in Dr. Hersey's declaration, there are over 5 million possible combinations in the disclosure in Heitz relied upon by Examiner. See Hersey Declaration ¶9. The claimed compound is merely 1 of those over 5 million. In accordance with Baird and Ortho-McNeil, the disclosure of millions of compounds in Heitz does not render the 1 claimed compound obvious. Further, as stated in MPEP 2144.08, the Federal Circuit requires that there be some reasonable likelihood of success for the proposed modification. Being 1 of over 5 million does

not provide any reasonable likelihood of success. As the Supreme Court stated in KSR, "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."

This is clearly not a example where routine experimentation would produce Applicants' claimed invention since, other than by blind luck, it would take one skilled in the art many lifetimes to use the disclosure in Heitz and arrive at any of the claimed compounds. See Hersey Declaration ¶9. This evidence rebuts the Examiner's conclusion. To overcome this evidence, the Examiner needs to produce evidence that this is routine experimentation. The general statements in the Office Action are not sufficient.

In addition, one of ordinary skill in the art would not have made the Examiner's hypothetical manipulation and modifications of the known halogenated xanthene dyes to arrive at the claimed invention, and there is no reason or motivation for one of ordinary skill in the art to make such modifications. More specifically, Heitz is concerned with certain optical properties of *known* halogenated xanthenes, and thus provides no reason or motivation for conceptualization or investigation of the highly-halogenated molecules of independent Claims 1, 36 and 37. See Hersey Declaration ¶10.

Furthermore, Heitz does not disclose or suggest the presently claimed therapeutic compositions or chemotherapeutic treatments. Instead of teachings directed to pharmaceutical compositions for treatment of diseases of human tissue (as is the subject of Applicants' claimed invention), Heitz is directed to *pesticidal compositions and their uses in livestock* (i.e., *ex vivo* killing of intestinal parasites to prevent infection, wherein the pathogenic organisms are killed by exposure to light outside of the infected animal before they can infect another animal). Heitz is not directed to

nor does it disclose or suggest an injectable chemotherapeutic composition for humans (as required in Claims 1, 36 and 37 of the present application). In fact, the subject matter of Heitz is so far afield from the subject matter of the claimed invention, that one skilled in the art would not be motivated in any way to rely or refer to this reference for compositions for treatment of diseases of human tissue, as in the claimed invention. See Hersey Declaration ¶11 and Ortho-McNeil at page 9.

For at least the above-stated reasons, Heitz fails to disclose or suggest the pharmaceutical compositions of the claimed invention, and the Examiner has failed to make out a prima facie case of obviousness. Even if a prima facie case has been established, Applicants have clearly rebutted it in this response, especially in light of the Declaration of Dr. Hersey evidencing the non-obviousness of the claimed invention.

Walker

As in the case of Heitz, Walker fails to disclose Applicants' claimed compound or compositions, and also fails to provide one of skill in the art any reason or motivation to discover or develop Applicants' claimed compound or compositions. For example, as described *supra*, Walker teaches away from compounds having any bromine substituents at positions 4, 5, 6 or 7, and certainly not bromine at each of these positions.

Moreover, Walker is concerned with compounds and compositions useful for phototrophic window coatings (i.e., that change color or density upon interaction with light), and thus represents a field completely unrelated and far afield to that of either Heitz or Applicants' invention (which are also unrelated to one another). Thus, one of skill in the art certainly would not be led to Applicants' invention upon any reading of Walker, alone or in combination with Heitz or any other prior art cited

in the present case.

Further, as the Supreme Court stated in KSR, a reason must be articulated for combining references as it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" (emphasis added). KSR, 127 S.Ct. at 1741. The Examiner cites no reason for combining Heitz and Walker, and certainly no reason to combine these references in the way the claimed invention does. Hence, this rejection and combination of references is improper.

Gee

As noted by Applicants in Amendment G in the present application, Gee concerns certain compositions containing *multiply-fluorinated* halogenated xanthenes. Gee does not disclose or suggest *any* halogenated xanthenes that do not contain fluorine. Since the claimed compound 4,5,6,7 tetrabromoerthrosin does not contain fluorine, Gee does not disclose or suggest the claimed compound. This was previously explained in Amendment G; after which, the Examiner apparently agreed and withdraw any rejections over Gee.

As the Examiner must admit, Gee does not specifically disclose 4,5,6,7-Tetrabromo-erythrosin. Instead, the Examiner appears to be basing this rejection on the general formula recited in Claim 3 in Gee and then making certain specific substitutions into that formula. However, such a rejection is clearly contrary to the patent laws and laws of nature.

In particular, the core structure that the Examiner cites in claim 3 of Gee appears to represent 2^{41} (i.e., ca. *2.2 trillion*) possibilities for just the combinations of functionalities at positions R1 and R6 (i.e., H + 4 halogens + 18 alkyl + 18 alkoxy groups at each of positions R1 and R6, ignoring

additional potential for unsaturation or variation in location of the cited oxygen groups). Given that there are fewer than 100 million compounds that have been identified in the history of chemistry, this comprises an extremely broad (in fact, overly broad) disclosure. In fact, while it is impossible to calculate the total number of possible combinations when including the other locations in the base molecule, it is for all intents and purposes infinity. Hence, application of this formula would render all chemical compounds anticipated or obvious, which is clearly contrary to the law.

> More specifically, it cannot be disputed that Gee does not specifically disclose Applicants' claimed compound. Moreover, the Examiner's use of the cited example structure in Gee as basis for rejection of Applicants' claims is improper under the patent laws and rules. See e.g. MPEP §2132.02

In the present case, Gee discloses a structure in claim 3, which is relied upon by the Examiner in the Office Action, that has well over *2.2 trillion* possible combinations, one of which is Applicants' claimed composition. This is not the limited class discussed in MPEP 2131.02. Instead, it represents more than a finite and small number of options, similar to the Ortho-McNeil case. Only through the use of hindsight reconstruction using the claimed compound as a blue print or endless experimentation and manipulation (which would take many lifetimes) could one skilled in the art arrive at the claimed compound from this disclosure in Gee.

Therefore, Gee does not explicitly disclose Applicants' novel compound, nor does Gee provide a workable roadmap that one of skill in the art could use to arrive at Applicants' novel compound.

Further, these *multiply-fluorinated* halogenated xanthenes compounds in Gee are purported to have utility as fluorescent dyes for certain in vitro tests. In contrast, the presently claimed compositions, which do not include *any* fluorinated halogenated xanthenes, are incorporated in chemotherapeutic pharmaceutical compositions which have been shown to have utility in vivo as

medicinal agents for chemotherapeutic purposes. Knowledge that one subset of halogenated xanthenes, such as those described by Gee, has utility for in vitro diagnostic use would not lead one of skill in the art to conclude that a separate, unrelated subset of halogenated xanthenes would have suitable pharmacokinetic and pharmacodynamic properties, when appropriately formulated, to serve as the active component in chemotherapeutic medicinal agents. Thus, one of skill in the art certainly would not be led to Applicants' invention upon any reading of Gee, alone or in combination with Heitz, Walker, or any other prior art cited in the present case.

Accordingly, the claims of the present application are not disclosed or suggested by the cited references, and the combination of references and rejections based thereon are improper and based on improper hindsight reconstruction. Therefore, the claims are clearly patentable, and it is respectfully requested that this rejection be withdrawn.

Information Disclosure Statement

Applicants are submitting an information disclosure statement (IDS) herewith to cite claims from other pending applications or issued patents for Applicants. It is respectfully requested that this IDS be entered and considered prior to the issuance of any further action on this application.

Interview Request

If the Examiner still wishes to reject the claims of the present application after considering this amendment, then Applicants request an interview with the Examiner to discuss the rejections in further depth. In such a case, it is respectfully requested that the Examiner contact the undersigned

to set-up such an interview prior to the issuance of a further Office Action for this application.

Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable condition and should be allowed.

If any fee should be due for this amendment or extension of time, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: April 2, 2008

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United States Court of Appeals for the Federal Circuit

2007-1223

ORTHO-MCNEIL PHARMACEUTICAL, INC.,

Plaintiff-Appellee,

v.

MYLAN LABORATORIES, INC.,
and MYLAN PHARMACEUTICALS, INC.,

Defendants-Appellants.

Harry J. Roper, Jenner & Block LLP, of Chicago, Illinois, argued for plaintiff-appellee. With him on the brief were Aaron A. Barlow and Eric L. Lohrenz, of Chicago, Illinois, and Marc A. Goldman, of Washington, DC.

David J. Harth, Heller Ehrman LLP, of Madison, Wisconsin, argued for defendants-appellants. With him on the brief were Randy J. Kozel, of Madison, Wisconsin, and Shannon M. Bloodworth, of Washington, DC.

Appealed from: United States District Court for the District of New Jersey

Judge Stanley R. Chesler

United States Court of Appeals for the Federal Circuit

2007-1223

ORTHO-MCNEIL PHARMACEUTICAL, INC.,

Plaintiff-Appellee,

v.

MYLAN LABORATORIES, INC.,
and MYLAN PHARMACEUTICALS, INC.

Defendants-Appellants.

Appeal from the United States District Court for the District of New Jersey in case no. 04-CV-1689, Judge Stanley R. Chesler.

DECIDED: March 31, 2008

Before MICHEL, Chief Judge, RADER and LINN, Circuit Judges.

RADER, Circuit Judge.

The United States District Court for the District of New Jersey permanently enjoined Mylan Laboratories, Inc. from infringing Ortho-McNeil Pharmaceutical Inc.'s U.S. Patent No. 4,513,006 ('006). The '006 patent claims the anticonvulsive drug topiramate. The trial court also reset the effective approval date for Mylan's Abbreviated New Drug Application (ANDA). Because the district court correctly ruled on claim construction, inequitable conduct, obviousness, and enablement, and because the district court did not err in resetting the effective date of Mylan's ANDA under 35 U.S.C. § 271(e)(4)(A), this court affirms.

I

Topiramate (marketed by Ortho-McNeil as TOPOMAX®) is a significant epilepsy drug with sales exceeding $1 billion annually. Ortho-McNeil scientist Dr. Bruce Maryanoff invented this pharmaceutical during a search for new antidiabetic drugs. Topiramate is a reaction intermediate in the synthesis Dr. Maryanoff ran as part of his antidiabetic efforts. Unexpectedly, Dr. Maryanoff discovered that this particular intermediate had powerful anticonvulsant properties. After extensive testing, clinical trials, and substantial investment, Ortho-McNeil showed that the compound was safe and effective leading to FDA approval.

This cause of action arose under the Hatch-Waxman Act. 21 U.S.C. § 355. Under that Act, Mylan filed an ANDA with the FDA with a paragraph IV certification asserting that Ortho-McNeil's '006 patent is invalid or not infringed. Within 45 days, Ortho-McNeil filed an infringement suit under 35 U.S.C. § 271(e)(2) against Mylan thus triggering the 30-month stay on approval of Mylan's ANDA.

After a Markman proceeding to set the meaning of the claim terms, the district court rejected Mylan's position that claim 1 of the '006 patent does not cover topiramate. Indeed, in light of the district court's claim construction ruling, Mylan stipulated that its generic topiramate infringes claims 1, 2, 4, 5, 6, 7, 8, 11 and 12 of the '006 patent. On summary judgment, the trial court also ruled against Mylan's affirmative defenses of unenforceability due to inequitable conduct and invalidity based on obviousness and non-enablement. After entry of final judgment, Mylan now appeals the district court's claim construction as well as the dismissal of its affirmative defenses of inequitable conduct, obviousness, and non-enablement.

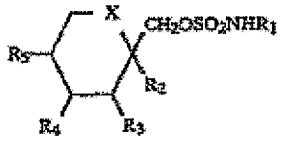
II

This court reviews a grant of summary judgment without deference. Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342, 1353 (Fed. Cir. 1998). This court must decide for itself "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R. Civ. P. 56(c); Celotex Corp. v. Catrett, 477 U.S. 317, 322 (1986). In deciding these questions, this court draws all justifiable inferences in the nonmovant's favor. Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 255 (1986). This court also reviews claim construction as a matter of law without deference. Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc).

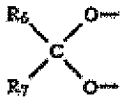
Mylan argues that the district court improperly construed the word *and* to mean *or* in independent claim 1, and under the proper construction, the claim does not cover topiramate. In light of the plain language of independent claim 1, several dependent claims, the specification, and the extrinsic evidence, this court sustains the trial court's ruling that, in the circumstances of this case, claim 1's use of the term *and* means *or.*

Claim 1 of the '006 patent states:

1. A sulfamate of the following formula (I):

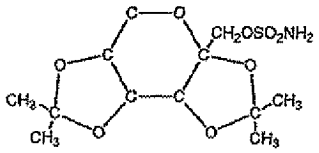


wherein
X is oxygen;
R1 is hydrogen or alkyl; and
R2, R3, R4 and R5 are independently hydrogen or lower alkyl and R2 and R3 and/or R4 and R5 together may be a group of the following formula (II):



wherein
R6 and R7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

Topiramate has the following structure:



In the molecule topiramate, R2 and R3 and R4 and R5 together are a group of formula (II), wherein R6 and R7 are methyl. Mylan argues that the use of the term *and* precludes the claim from encompassing topiramate. In context, the term *and* falls between several R group recitations:

> R2, R3, R4, and R5 are independently hydrogen or lower alkyl *and* R2 and R3 and/or R4 and R5 together may be a group of formula (II) (emphasis added).

On this basis, Mylan argues that the phrase quoted above contains two independent claim limitations: (1) that "R2, R3, R4, and R5 are independently hydrogen or lower alkyl" *and* (2) that "R2 and R3 and/or R4 and R5 together may be a group of formula (II)." Under Mylan's construction, both of these limitations must be met in order for a compound to infringe. Both of these limitations are not met in topiramate. None of the R2, R3, R4, and R5 subunits are hydrogen or lower alkyl because both R2 and R3 and R4 and R5 together are a group of formula (II).

To the contrary, the claim language depicts two subsets of compounds, but does not require their simultaneous existence. In one subset of compounds covered by claim

1, the groups R2, R3, R4, and R5 are independent of one another, in which case, according to the claim, they are either hydrogen or lower alkyl. In a second subset of compounds covered by claim 1, the R2 through R5 groups are not independent, but rather R2 and R3 are together, and/or R4 and R5 are together, to form either one or two groups of formula (II). Topiramate is an example of this type of compound. In it, R2 and R3 are arranged together in a group, as are R4 and R5. Thus, as used in this claim, *and* conjoins mutually exclusive possibilities.

The claim also does not use *and* in isolation but in a larger context that clarifies its meaning. Specifically, *and* appears in conjunction with the adverbs *independently* and *together.* As the district court explained, these terms signal that *and* links alternatives that occur under the different conditions of independence or togetherness. In context, it is clear that one of the subunits (R2, R3, R4, or R5) does not always have to be either a hydrogen or lower alkyl.

The larger context of this patent also supports this claim meaning. Construing claim 1 to require a conjunctive meaning of *and* would render several dependent claims meaningless. Claims 2, 5, 9, and 10 would cover nothing if the *and* at issue must be conjunctive. This court has explained: "Other claims of the patent in question . . . can also be valuable sources of enlightenment as to the meaning of a claim term." Phillips v. AWH Corp., 415 F.3d 1303, 1314 (Fed. Cir. 2005) (en banc) (citing Vitronics Corp. v. Conceptronic Inc., 90 F.3d 1576, 1582 (Fed. Cir. 2003)). Thus, this court strives to reach a claim construction that does not render claim language in dependent claims meaningless. Rambus Inc. v. Infineon Tech. AG, 318 F.3d 1081, 1093 (Fed. Cir. 2003).

The specification also supports the district court's reading of *and*. The specification thus uses the word *and* to link alternative chemical structures. In column 1 lines 47-50 the specification provides:

> R2, R3, R4 and R5 are independently hydrogen or lower alkyl *and*, when X is CH2, R4 and R5 may be alkene groups joined to form a benzene ring *and* when X is oxygen, R2 and R3 and/or R4 and R5 together may be a methylenedioxy group of the following formula II . . . .

(emphases added). Without question, this passage within the specification shows use of the word *and* to join alternatives.

While extrinsic evidence "can shed useful light on the relevant art," this court considers such evidence "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" Phillips, 415 F.3d at 1317 (citations omitted). Because the plain language of claim 1, the dependent claims, and the specification support the district court's reading, this court does not need to consult extrinsic evidence. Nonetheless, this court notes that dictionary definitions of *and*, while most often listing the additive sense as the most common usage of the term, also show usage of the term to connote alternatives. Webster's Third New International Dictionary (2002). In the circumstances of this case, the use of *and* to express alternatives was chosen and adequately expressed by the applicant. Thus, extrinsic evidence too offers support for the district court's reading of the disputed term.

In Chef America Inc. v. Lamb-Weston, Inc., this court explained that a patent must be interpreted "as written, not as the patentees wish they had written it." 358 F.3d 1371, 1374 (Fed. Cir. 2004). In other words, courts may not redraft claims, whether to make them operable or to sustain their validity. Id. Even "a nonsensical result does not

require the court to redraft the claims of the . . . patent." Id. (citing Process Control Corp. v. HydReclaim Corp., 190 F.3d 1350, 1357 (Fed. Cir. 1999)). However, Chef America does not require this court or the district court to interpret *and* according to its most common usage in the dictionary. To the contrary, this court and the district court must interpret the term to give proper meaning to the claim in light of the language and intrinsic evidence. Giving *and* its most common dictionary meaning would produce in this case the nonsensical result of not covering topiramate and rendering several other dependent claims meaningless. In Chef America, the only possible interpretation of the claim led to a nonsensical result. This situation is distinguishable because claim 1 can and should be interpreted as the patentees intended, with the meaning of *and* connoting alternatives.

In sum, the district court properly interpreted the claim. This court detects no error in its claim construction.

III

Mylan accuses Ortho-McNeil of committing inequitable conduct by failing to disclose the results of non-public tests it conducted on the prior art Kochetkov compounds to the Patent Office. In fact, the applicant submitted the Kochetkov references themselves, but not results from the tests that Dr. Maryanoff conducted on the compounds. Mylan says that Ortho-McNeil's statements about the Kochetkov references during prosecution were inconsistent with Ortho-McNeil's own information that the compounds had anticonvulsant properties. During prosecution, Ortho-McNeil said the following:

> It should be noted that the utility disclosed in the Kochetkov references AR-AU is extremely limited and narrow. These compounds are merely

> taught as being convenient derivatives of monosaccharide sulfates to allow separation of such sulfates from each other with regeneration of the original sulfate thereafter. No teaching is provided for any actual utility of the sulfamates or sulfates described in AR-AU and it is respectfully submitted that there is no motivation for one skilled in the art reading AR-AU to go beyond the pyranoses disclosed therein to arrive at Applicant's invention.

Mylan claims that this was a misrepresentation because in-house test results demonstrated that the Kochetkov compounds had anticonvulsive properties. To the contrary, the district court found, and this court agrees, that Ortho-McNeil did not make misrepresentations to the Patent Office during prosecution. The quoted passage merely accurately characterizes the references as claiming limited utility for the Kochetkov compounds. Ortho-McNeil made no assertions about the compounds themselves, but only repeated the disclosures of the Kochetkov references.

The same observation applies to the sentence following the passage quoted above:

> As explained above, the pyranoses of AR-AU are entirely different in structure and use than the pyranoses of the present invention, and given the minimal usefulness of the AR-AU compounds, it would not be obvious to one skilled in the art to go beyond AR-AU to the pyranose structures of the present invention.

Again, as the opening phrase of the above quote confirms, the applicant is repeating the disclosures of the Kochetcov references, not characterizing the compounds themselves. Read in context, the Kochetkov references do not disclose any utility. On this point, the applicant is correct. Moreover, the applicant did not assert that the compounds themselves possess no utility. Thus, Ortho-McNeil made no misrepresentations to the Patent Office. Accordingly the district court correctly dismissed Mylan's affirmative defense of inequitable conduct.

IV

Dr. Laurens Anderson, Mylan's expert, asserts that a person of ordinary skill in the art faced with finding a diabetes drug (as Dr. Maryannoff was) would necessarily design an FBPase inhibitor. Mylan cites KSR International Co. v. Teleflex Inc., for the proposition that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." 127 S. Ct. 1727, 1742 (2007). The record, however, shows that even if an ordinarily skilled artisan sought an FBPase inhibitor, that person would not have chosen topiramate. Moreover this invention, contrary to Mylan's characterization, does not present a finite (and small in the context of the art) number of options easily traversed to show obviousness. The passage above in KSR posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness. In this case, the record shows that a person of ordinary skill would not even be likely to start with 2,3:4,5 di-isopropylidene fructose (DPF), as Dr. Maryanoff did. Beyond that step, however, the ordinarily skilled artisan would have to have some reason to select (among several unpredictable alternatives) the exact route that produced topiramate as an intermediate. Even beyond that, the ordinary artisan in this field would have had to (at the time of invention without any clue of potential utility of topiramate) stop at that intermediate and test it for properties far afield from the purpose for the development in the first place (epilepsy rather than diabetes). In sum, this clearly is not the easily traversed, small and finite number of

alternatives that KSR suggested might support an inference of obviousness. Id. at 1742.

In other words, Mylan's expert, Dr. Anderson, simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate was obvious. Of course, this reasoning is always inappropriate for an obviousness test based on the language of Title 35 that requires the analysis to examine "the subject matter as a whole" to ascertain if it "would have been obvious at the time the invention was made." 35 U.S.C. § 103(a) (emphasis added). In retrospect, Dr. Maryanoff's pathway to the invention, of course, seems to follow the logical steps to produce these properties, but at the time of invention, the inventor's insights, willingness to confront and overcome obstacles, and yes, even serendipity, cannot be discounted.

Speaking before KSR, the district court endorsed a "rigorous application" of the teaching, suggestion, or motivation (TSM) test. In KSR, the Supreme Court explained that a "rigid" TSM test "is incompatible with our precedents." KSR, 127 S. Ct. at 1741. Mylan thus contends that the district court erred by rigorously applying the TSM test. The Supreme Court explained its reason for castigating a "rigid" TSM test: "The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents." Id. Indeed a rigid requirement of reliance on written prior art or patent references would, as the Supreme Court noted, unduly confine the use of the knowledge and creativity within the grasp of an ordinarily skilled artisan. Id. at 1742.

As this court has explained, however, a flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis such as occurred in this case. In re Translogic Tech., Inc., 504 F.3d 1249, 1257 (Fed. Cir. 2007) ("[A]s the Supreme Court suggests, a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of invention."). The TSM test, flexibly applied, merely assures that the obviousness test proceeds on the basis of evidence – teachings, suggestions (a tellingly broad term), or motivations (an equally broad term) – that arise before the time of invention as the statute requires. As KSR requires, those teachings, suggestions, or motivations need not always be written references but may be found within the knowledge and creativity of ordinarily skilled artisans.

In this case, the record amply supports the district court's finding of nonobviousness. This court detects no rigid application of the evidentiary requirements for obviousness in the district court's analysis. As noted above, the challenges of this inventive process would have prevented one of ordinary skill in this art from traversing the multiple obstacles to easily produce the invention in light of the evidence available at the time of invention. Of particular importance beyond the prima facie analysis, this court also detects evidence of objective criteria showing nonobviousness. Specifically, the record shows powerful unexpected results (anticonvulsive activity) for topiramate. The record also shows skepticism of experts and copying – other respected sources of objective evidence of nonobviousness – as well as commercial success. As this court has repeatedly explained, this evidence is not just a cumulative or confirmatory part of the obviousness calculus but constitutes independent evidence of nonobviousness. Catalina Lighting, Inc. v. Lamps Plus, Inc., 295 F.3d 1277, 1288 (Fed. Cir. 2002)

("Objective indicia may often be the most probative and cogent evidence of nonobviousness in the record.") (internal citation omitted). See also Pharmastem Therapeutics Inc. v. Viacell, Inc., 491 F.3d 1342; Eli Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369.

Mylan asserts that method of use claims 6-8 are also obvious. But if claim 1 is not obvious then claims 6-8 also cannot be obvious because they all depend from a nonobvious claim. In re Fritch, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ("[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious."). Accordingly, the method of use claims are nonobvious as well.

V

Mylan asserts that claims 6-8 are not enabled because an *anticonvulsively effective* amount is unclear and its determination would require undue experimentation. A specification that enables an invention will teach those ordinarily skilled in the art to make and use the full scope of the claimed invention without undue experimentation. Genentech Inc. v. Novo Nordisk of N. Am. Inc., 108 F.3d 1361, 1365 (Fed. Cir. 1997).

The '006 specification discloses that the average adult requires 30-2000 milligrams of the claimed compounds administered in two to four doses of 10-500 milligrams. The specification also teaches a skilled artisan to use the claimed compounds in a manner similar to the drug phenytoin. Further the specification directs the reader to a reference by L.S. Goodman, which teaches that after establishment of a low initial dose, the dosage is increased at appropriate intervals as required for control of seizures or as limited by toxicity with further adjustments according to plasma drug concentrations. L.S. Goodman, et al., The Pharmacological Basis of Therapeutics, 201-

26 (5th ed. 1975). This court sustains the district court's judgment that this disclosure adequately enables claims 6-8. Further, even if clinical trials informed the anticonvulsively effective amount, this record does not show that extensive or "undue" tests would be required to practice the invention. The district court was correct in summarily dismissing Mylan's non-enablement defense.

VI

When a generic manufacturer files an ANDA with a paragraph IV certification, Hatch-Waxman grants the brand name pharmaceutical manufacturer a 30-month stay in the approval of that ANDA within which to litigate its case. 21 U.S.C. § 355(j)(5)(B)(iii). At the expiration of the 30 months, the ANDA is automatically approved unless the court grants a preliminary injunction or finds infringement. Because neither of those two events occurred before expiration of 30 months, the FDA approved Mylan's ANDA by operation of law. Therefore, after determining infringement, the district court reset the effective date of approval pursuant to 35 U.S.C. § 271(e)(4)(A), which provides:

> (4) For an act of infringement described in paragraph (2)
> (A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed.

Although the statute does not expressly reset the effective date when the 30-month stay expires before the patent is found to be infringed or a preliminary injunction granted, the statute, as informed by its legislative history, supports the district court's action of resetting the effective date. The House Report accompanying the Hatch-Waxman Act explains: "[I]n the case where an ANDA had been approved, the order

would mandate a change in the effective date." H.R. Rep. No. 98-857, at 46 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2679.

Mylan argues that the district court's order is inconsistent with 21 U.S.C. § 355(j)(5)(B)(iii), which lays out two measures for delaying an ANDA's approval:

> 21 U.S.C. § 355(j)(5)(B)(iii)(II)(bb) provides: if the district court decides that the patent has been infringed before the expiration of the 30 month period, then the FDA's approval shall be made effective on the date specified by the district court in a court order under 35 U.S.C. § 271(e)(4)(A).
>
> 21 U.S.C. § 355(j)(5)(B)(iii)(IV) provides: if before the expiration of [the 30 month stay] the court grants a preliminary judgment . . . and if the court decides that such patent has been infringed then the approval shall be made effective as in subclause (II).

The district court, however, did not ignore these express conditions when resetting the effective date. Considering 35 U.S.C. § 271, the district court correctly discerned that the provisions quoted above do not limit the authority of the district court to reset the effective date in circumstances similar to those statutorily listed as indeed suggested by the legislative history for the provision. Indeed 21 U.S.C. § 355 does not limit a court's authority to reset for conditions other than those listed. This provision, directed at the FDA, instructs the agency regarding its responsibilities to process an ANDA. This provision does not limit the court's authority as noted. The district court was correct to reset the effective date of an ANDA directly under 35 U.S.C. § 271 without going through 21 U.S.C. § 355.

VII

In view of all the intrinsic and extrinsic evidence, the district court correctly construed claim 1 to cover Ortho-McNeil's epilepsy drug topiramate. Accordingly, this

court affirms the district court's decision to permanently enjoin Mylan from infringing the '006 patent. This court also affirms the dismissal of Mylan's invalidity defenses based on obviousness, inequitable conduct, and non-enablement and finds no error in the district court's decision to reset the effective date of Mylan's ANDA to a date not earlier than the date of expiration of the patent.

AFFIRMED